(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 October 2002 (24.10.2002)

PCT

(10) International Publication Number
WO 02/083111 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/JP02/03723

(22) International Filing Date: 15 April 2002 (15.04.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2001-116436 16 April 2001 (16.04.2001) JP
2001-249671 20 August 2001 (20.08.2001) JP

(71) Applicant *(for all designated States except US)*: **TANABE SEIYAKU CO., LTD.** [JP/JP]; 2-10 Dosho-Machi 3-Chome, Chuo-Ku, Osaka 541-8505 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HONGU, Mitsuya** [JP/JP]; 2486-25, Ohaza-Haraichi,, Ageo-Shi, Saitama 362-0021 (JP). **HOSAKA, Thoshihiro** [JP/JP]; 2-7 Higashi-ueno 2-chome, Taitou-ku, Tokyo 110-0015 (JP). **KASHIWAGI, Toshihiko** [JP/JP]; 3-8 Kawagishi 2-chome, Toda-shi, Saitama 335-0015 (JP). **KONO, Rikako** [JP/JP]; Towa City Coop 401, 180-1 Sakuragicho 4-chome, Saitama-shi, Saitama 331-0852 (JP). **KOBAYASHI, Hiroyuki** [JP/JP]; 1127-1-B, Ohaza-Angyo-Jirin, Kawaguchi-shi,, Saitama 334-0071 (JP).

(74) Agent: **TSUKUNI, Hajime**; Svax TS Building, 22-12, Toranomon 1-chome, Minato-ku, Tokyo 105-0001 (JP).

(81) Designated States *(national)*: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL, RO, SG, SI, SK, TN, TT, UA, US, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

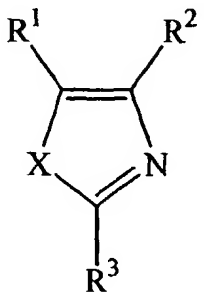
Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

102(a)

1-5

(54) Title: LARGE CONDUCTANCE CALCIUM-ACTIVATED K CHANNEL OPENER



(I)

(57) Abstract: A large conductance calcium-activated K channel opener comprising as an active ingredient a nitrogen-containing 5-membered heterocyclic compound represented by the following formula (I): wherein X represents N-R^4, O or S, R^1 and R^2 each independently represent hydrogen, halogen, carboxyl, amino, lower alkyl, lower alkoxycarbonyl, lower alkenyl, cyclo-lower alkyl, carbamoyl, aryl, heterocyclic or heterocyclic-substituted carbonyl group, R^3 represents aryl, heterocyclic or lower alkyl group, and R^4 represents hydrogen or lower alkyl group.

WO 02/083111 A2

DESCRIPTION

LARGE CONDUCTANCE CALCIUM-ACTIVATED K CHANNEL OPENER

FIELD OF THE INVENTION

This invention relates to an excellent large conductance calcium-activated K channel opener containing a nitrogen-containing 5-membered heterocyclic compound as an active ingredient, which is useful for treatment of disorders or diseases such as pollakiuria, urinary incontinence, cerebral infarction, subarachnoid hemorrhage, and the like.

BACKGROUND OF THE INVENTION

Potassium is the most abundant intracelluar cation, and is very important in maintaining physiological homeostasis. Potassium channels are present in almost all vertebrate cells, and the potassium influx through these channels is indispensable for maintaining hyperpolarized resting membrane potential.

Large conductance calcium activated potassium channels (also BK channels or maxi-K channels) are expressed especially in neurons and smooth muscle cells. Because both of the increase of intracellular calcium concentration and membrane depolarization can activate maxi-K channels, maxi-K channels have been thought to play a pivotal role in regulating voltage-dependent calcium influx. Increase in the intracellular calcium concentration mediates many processes such as release of neurotransmitters, contraction of smooth muscles, cell growth and death, and the like. Actually, the opening of maxi-K channels causes strong membrane hyperpolarization, and inhibits these calcium-induced responses thereby. Accordingly, by inhibiting various depolarization-mediated

Table 1 (contd.)

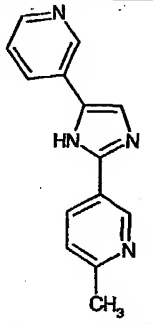
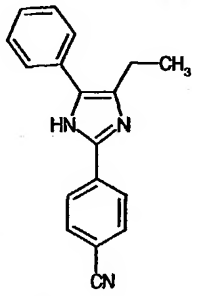
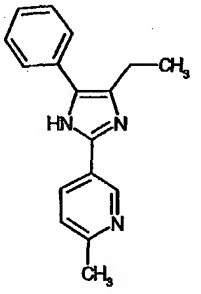
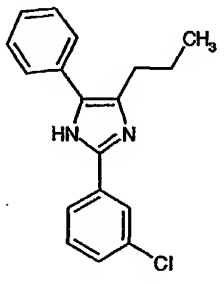
Preparation example No.	Chemical structure	Salt	Physical constant, etc.
26		3HCl	Crystal Melting point: 269-273°C MS·APCI(m/z): 237(M+H)+
27		1HCl	Crystal Melting point: 285-288°C MS·APCI(m/z): 274(M+H)+
28		2HCl	Crystal Melting point: 248-251°C MS·APCI(m/z): 264(M+H)+
29		1HCl	Crystal Melting point: 202-204°C MS·APCI(m/z): 297(M+H)+

Table 1 (contd.)

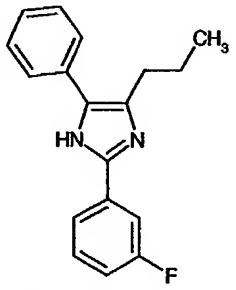
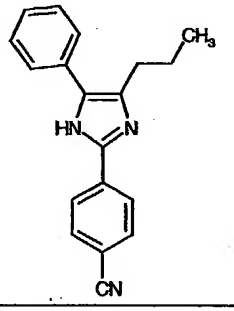
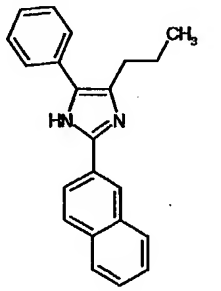
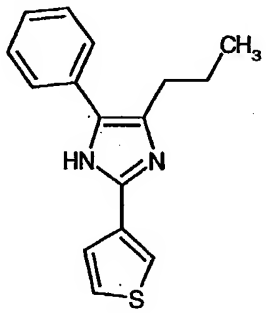
Preparation example No.	Chemical structure	Salt	Physical constant, etc.
30		1HCl	Crystal Melting point: 192-193°C MS·APCI(m/z): 281(M+H)+
31		1HCl	Crystal Melting point: 258-260°C MS·APCI(m/z): 288(M+H)+
32		1HCl	Crystal Melting point: 189-190°C MS·APCI(m/z): 313(M+H)+
33		1HCl	Crystal Melting point: 215-217°C MS·APCI(m/z): 269(M+H)+

Table 2 (contd.)

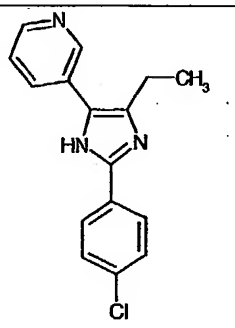
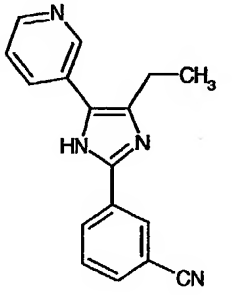
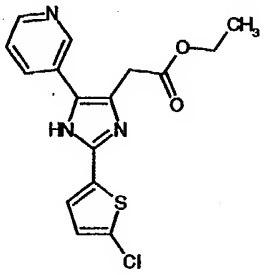
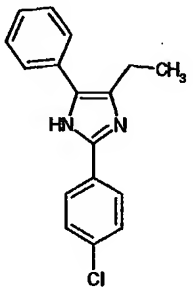
Preparation example No.	Chemical structure	Salt	Physical constant, etc.
56		2HCl	Powder MS·APCI(m/z): 284(M+H)+
57		2HCl	Powder MS·APCI(m/z): 275(M+H)+
58		2HCl	Powder MS·APCI(m/z): 348(M+H)+
59		Free material	Crystal Melting point: 174-176°C EI·MS(m/z): 282/284(M+)

Table 2 (contd.)

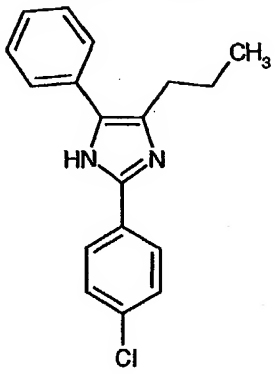
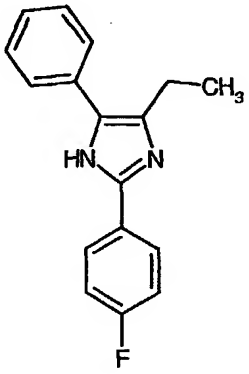
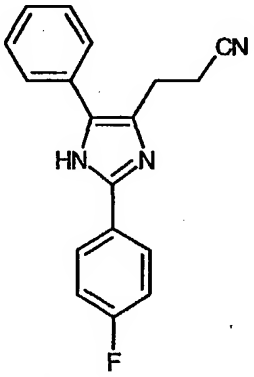
Preparation example No.	Chemical structure	Salt	Physical constant, etc.
60		Free material	Crystal Melting point: 147-149°C EI·MS(m/z): 297/299(M+)
61		Free material	Crystal Melting point: 169-170°C EI·MS(m/z): 266(M+)
62		Free material	Crystal Melting point: 176-178°C EI·MS(m/z): 291(M+)

Table 8

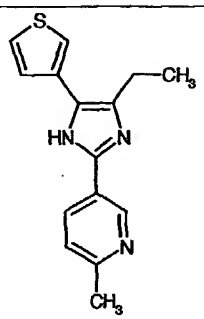
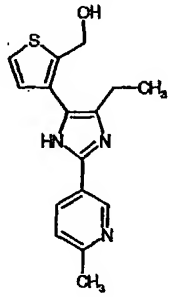
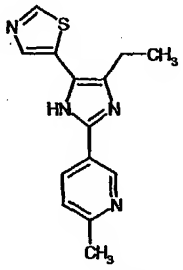
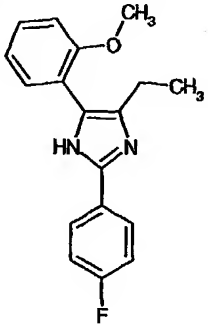
Preparation example No.	Chemical structure	Salt	Physical constant, etc.
81		2HCl	Solid MS·APCI(m/z): 270(M+H)+
82		2HCl	Solid MS·APCI(m/z): 300(M+H)+
83		2HCl	Crystal Melting point: 247-251°C MS·APCI(m/z): 271(M+H)+
84		1HCl	Crystal Melting point: 200-203°C (Decomposed) MS·APCI(m/z): 297(M+H)+

Table 8 (contd.)

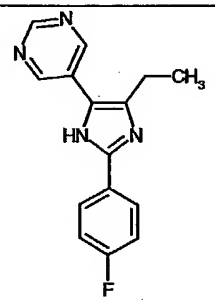
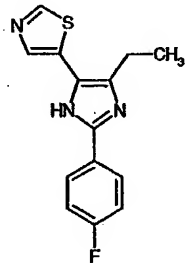
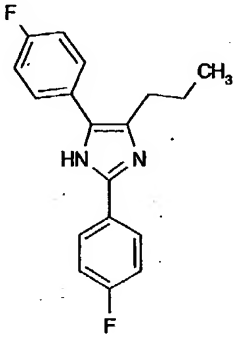
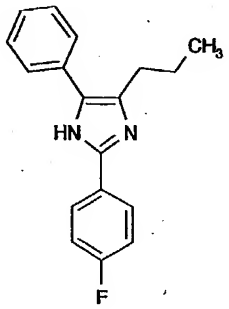
Preparation example No.	Chemical structure	Salt	Physical constant, etc.
85		1HCl	Crystal Melting point: 287-289°C MS·APCI(m/z): 269(M+H)+
86		1HCl	Crystal Melting point: 254-256°C MS·APCI(m/z): 274(M+H)+
87		1HCl	Crystal Melting point: 233-235°C MS·APCI(m/z): 299(M+H)+
88		1HCl	Crystal Melting point: 224-226°C MS·APCI(m/z): 281(M+H)+

Table 8 (contd.)

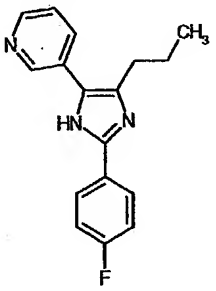
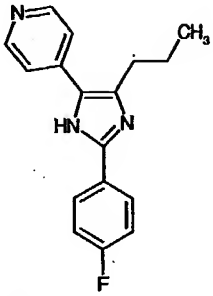
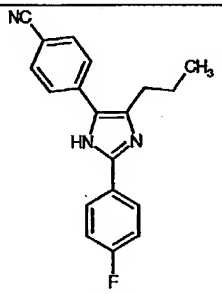
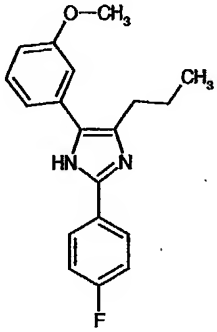
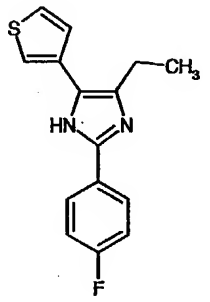
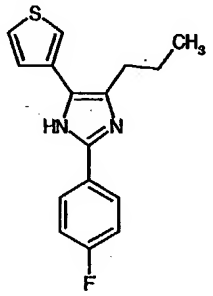
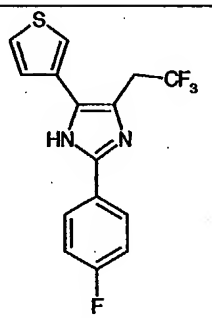
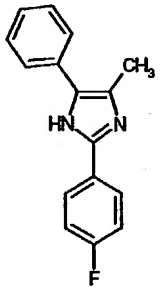
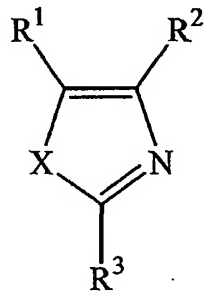
Preparation example No.	Chemical structure	Salt	Physical constant, etc.
93		2HCl	Powder MS·APCI(m/z): 282(M+H)+
94		2HCl	Powder MS·APCI(m/z): 282(M+H)+
95		Free material	Crystal Melting point: 240-242°C MS·APCI(m/z): 306(M+H)+
96		1HCl	Crystal Melting point: 120-122°C MS·APCI(m/z): 311(M+H)+

Table 16 (contd.)

Preparation example No.	Chemical structure	Salt	Physical property, etc.
171		Free material	MS·EI(m/z): 272(M+)
172		Free material	MS·EI(m/z): 286(M+)
173		Free material	MS·EI(m/z): 326(M+)
174		Free material	MS·EI(m/z): 252(M+)

Claims:

1. A large conductance calcium-activated K channel opener comprising as an active ingredient a nitrogen-containing 5-membered heterocyclic compound represented by the following formula (I):



(I)

wherein X represents N-R^4, O or S, R^1 and R^2 are different from each other and each independently represents hydrogen atom, a halogen atom, carboxyl group, a substituted or unsubstituted amino group, a substituted or unsubstituted lower alkyl group, a lower alkoxycarbonyl group, a substituted or unsubstituted lower alkenyl group, a cyclo-lower alkyl group, a substituted or unsubstituted carbamoyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted heterocyclic group-substituted carbonyl group, R^3 represents a substituted or unsubstituted aryl group, a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted lower alkyl group, and R^4 represents hydrogen atom or a substituted or unsubstituted lower alkyl group, or a pharmaceutically acceptable salt thereof.

2. The large conductance calcium-activated K channel opener according to Claim 1, wherein R^1 and R^2 each independently represent (1) hydrogen atom, (2) a halogen atom, (3) a carboxyl group, (4) an amino group which may be substituted by at least

one selected from formyl group, a lower alkyl group, a lower alkanoyl group, a lower alkylsulfonyl group and a lower alkoxycarbonyl group, (5) a lower alkyl group which may be substituted by at least one selected from a halogen atom, hydroxyl group, cyano group, carboxyl group, carbamoyl group, amino group, aminosulfonyl group, a halogenosulfonyl group, amidinothio group, a mono- or di-lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, hydroxyamino group, a mono- or di-lower alkylcarbamoyl group, trifluoromethyl group, a lower alkoxy group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a lower alkoxycarbamoyl group, a lower alkylsulfonylcarbamoyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkoxycarbonyl group, a heterocyclic group, a heterocyclic group-substituted carbamoyl group, a heterocyclic group-substituted lower alkylcarbamoyl group and a heterocyclic group-substituted sulfonylcarbamoyl group, (6) a lower alkoxycarbonyl group, (7) a lower alkenyl group which may be substituted by carboxyl group or a lower alkoxycarbonyl group, (8) a cyclo-lower alkyl group, (9) a carbamoyl group which may be substituted by at least one selected from a lower alkyl group, a lower alkoxy group and a lower alkylsulfonyl group, (10) an aryl group which may be substituted by at least one selected from nitro group, amino group, hydroxyl group, carbamoyl group, cyano group, carboxyl group, trifluoromethyl group, a lower alkoxycarbonyl group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxy-lower alkoxy group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkylsulfonylamino group and a phenyl-lower alkoxy group, (11) a heterocyclic group which may be substituted by at least one selected from nitro group, hydroxyl group, formyl group, carbamoyl group, cyano group, amino group, carboxyl group, a lower alkoxycarbonyl

group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group and a mono- or di-lower alkylsulfamoyl group, or (12) a heterocyclic group-substituted carbonyl group which may be substituted by at least one selected from nitro group, hydroxyl group, carbamoyl group, cyano group, carboxyl group, a lower alkoxycarbonyl group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkanoyl group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group and a mono- or di-lower alkylsulfamoyl group; R^3 is (1) an aryl group which may be substituted by at least one selected from cyano group, nitro group, amino group, a halogen atom, trifluoromethyl group, carboxyl group, hydroxyl group, carbamoyl group, a mono- or di-lower alkylamino group, a mono- or di-lower alkylamino-lower alkyl group, a mono- or di-lower alkylcarbamoyl group, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group, a lower alkanoyl group, a lower alkanoyloxy group, a lower alkanoyloxy-lower alkyl group, sulfo group, a lower alkylthio group, a lower alkylthio-lower alkyl group, a lower alkylsulfonyl group, a lower alkylsulfamoyl group and a lower alkylsulfinyl group, (2) a heterocyclic group which may be substituted by at least one selected from oxo group, cyano group, nitro group, amino group, a halogen atom, carboxyl group, hydroxyl group, formyl group, carbamoyl group, a mono- or di-lower alkylamino group, a N-lower alkyl-N-cyclo-lower alkylamino group, a mono- or di-lower alkylamino-lower alkyl group, a mono- or di-lower alkylcarbamoyl group, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxy-lower alkyl group, a lower alkoxycarbonyl group, a lower alkanoyl group, sulfo group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfamoyl group, a

lower alkylsulfinyl group and a heterocyclic group, or (3) a alkyl group which may be substituted by at least one selected from hydroxyl group, cyano group, carboxyl group, carbamoyl group, amino group, a mono- or di-lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, hydroxyamino group, a mono- or di-lower alkylcarbamoyl group, trifluoromethyl group, a halogen atom, a lower alkoxy group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkoxycarbonyl group and a heterocyclic group; and R^4 is (1) hydrogen atom, or (2) a lower alkyl group which may be substituted by a mono- or di-lower alkylamino group.

3. The large conductance calcium-activated K channel opener according to Claim 1 or 2, wherein R^1 is (1) a lower alkyl group which may be substituted by carboxyl group, a lower alkoxycarbonyl group or a heterocyclic group, (2) an aryl group which may be substituted by one or two halogen atoms, or (3) a heterocyclic group which may be substituted by a halogen atom, R^2 is (1) a lower alkyl group which may be substituted by carboxyl group, a lower alkoxycarbonyl group or a heterocyclic group, (2) a heterocyclic group which may be substituted by a halogen atom, or (3) an aryl group which may be substituted by one or two halogen atoms; R^3 is (1) a heterocyclic group which may be substituted by one or two groups selected from amino group, a halogen atom, a lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group and a lower alkylthio group, or (2) an aryl group which may be substituted by amino group, a halogen atom, a lower alkyl group, a lower alkylthio group, a lower alkoxy group or a mono- or di-lower alkylamino group; and R^4 is hydrogen atom or a lower alkyl group.

4. The large conductance calcium-activated K channel opener according to Claim 3, wherein R^1 is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3) a lower

alkyl group substituted by a tetrazolyl group, (4) a phenyl group which may be substituted by one or two halogen atoms, or (5) a thienyl group which may be substituted by a halogen atom; R^2 is (1) a carboxyl-lower alkyl group, (2) a lower alkoxy-carbonyl-lower alkyl group, (3) a lower alkyl group substituted by a tetrazolyl group, (4) a thienyl group which may be substituted by a halogen atom, or (5) a phenyl group which may be substituted by one or two halogen atoms; and R^3 is (1) a benzothienyl group which may be substituted by a halogen atom, (2) a phenyl group which may be substituted by a halogen atom, a lower alkylthio group, a lower alkoxy group or a di-lower alkylamino group, (3) a pyridyl group which may be substituted by a lower alkyl group, a lower alkoxy group or a di-lower alkylamino group, (4) a pyrimidinyl group which may be substituted by a di-lower alkylamino group or a lower alkylthio group, (5) a thienyl group which may be substituted by one or two lower alkyl groups, (6) thieno[3,2-b]pyridyl group, (7) benzofuryl group, (8) dihydrobenzofuryl group or (9) an indolyl group which may be substituted by a lower alkyl group.

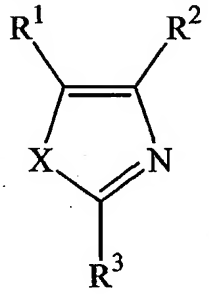
5. The large conductance calcium-activated K channel opener according to Claim 4, wherein X is O or S; R^1 is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3) a phenyl group which may be substituted by one or two halogen atoms, or (4) a thienyl group which may be substituted by a halogen atom; R^2 is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3) a thienyl group which may be substituted by a halogen atom, or (4) a phenyl group which may be substituted by one or two halogen atoms; and R^3 is (1) a benzothienyl group which may be substituted by a halogen atom, (2) a phenyl group which may be substituted by a halogen atom, a lower alkylthio group, a lower alkoxy group or a di-lower alkylamino group, (3) a pyridyl group which may be substituted by a lower alkoxy group or a di-lower alkylamino group, (4) a pyrimidinyl group which may be substituted by a di-lower alkylamino group, (5) a thienyl group

which may be substituted by a di-lower alkyl group, (6) thieno[3,2-b]pyridyl group, or (7) an indolyl group which may be substituted by a lower alkyl group.

6. Use of the large conductance calcium-activated K channel opener as set foth in any one of Claims 1 to 5 for manufacture of a medicament for use in the treatment or prophylaxis of pollakiuria or urinary incontinence.

7. A method for prophylaxis and/or treatment of pollakiuria or urinary incontinence which comprises administering an effective amount of the large conductance calcium-activated K channel opener as set forth in any one of Claims 1 to 5 to a patient of pollakiuria or urinary incontinence or a patient who has a possibility of causing pollakiuria or urinary incontinence.

8. Use of a compound of formula (I)



(I)

wherein X represents N-R^4, O or S, R^1 and R^2 are different from each other and each independently represents hydrogen atom, a halogen atom, carboxyl group, a substituted or unsubstituted amino group, a substituted or unsubstituted lower alkyl group, a lower alkoxycarbonyl group, a substituted or unsubstituted lower alkenyl group, a cyclo-lower alkyl group, a substituted or unsubstituted carbamoyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted heterocyclic group-substi-

tuted carbonyl group, R^3 represents a substituted or unsubstituted aryl group, a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted lower alkyl group, and R^4 represents hydrogen atom or a substituted or unsubstituted lower alkyl group,
or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in the treatment or prophylaxis of pollakiuria or urinary incontinence.

9. The use according to Claim 8, wherein R^1 and R^2 each independently represent (1) hydrogen atom, (2) a halogen atom, (3) a carboxyl group, (4) an amino group which may be substituted by at least one selected from formyl group, a lower alkyl group, a lower alkanoyl group, a lower alkylsulfonyl group and a lower alkoxycarbonyl group, (5) a lower alkyl group which may be substituted by at least one selected from a halogen atom, hydroxyl group, cyano group, carboxyl group, carbamoyl group, amino group, aminosulfonyl group, a halogenosulfonyl group, amidinothio group, a mono- or di-lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, hydroxyamino group, a mono- or di-lower alkylcarbamoyl group, trifluoromethyl group, a lower alkoxy group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a lower alkoxycarbamoyl group, a lower alkylsulfonylcarbamoyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkoxycarbonyl group, a heterocyclic group, a heterocyclic group-substituted carbamoyl group, a heterocyclic group-substituted lower alkylcarbamoyl group and a heterocyclic group-substituted sulfonylcarbamoyl group, (6) a lower alkoxycarbonyl group, (7) a lower alkenyl group which may be substituted by carboxyl group or a lower alkoxycarbonyl group, (8) a cyclo-lower alkyl group, (9) a carbamoyl group which may be substituted by at least one selected from a lower alkyl group, a lower alkoxy group and a lower alkylsulfonyl group, (10) an aryl group which may be substituted by at least one selected from nitro group, amino

group, hydroxyl group, carbamoyl group, cyano group, carboxyl group, trifluoromethyl group, a lower alkoxycarbonyl group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxy-lower alkoxy group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkylsulfonylamino group and a phenyl-lower alkoxy group, (11) a heterocyclic group which may be substituted by at least one selected from nitro group, hydroxyl group, formyl group, carbamoyl group, cyano group, amino group, carboxyl group, a lower alkoxycarbonyl group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group and a mono- or di-lower alkylsulfamoyl group, or (12) a heterocyclic group-substituted carbonyl group which may be substituted by at least one selected from nitro group, hydroxyl group, carbamoyl group, cyano group, carboxyl group, a lower alkoxycarbonyl group, a halogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkanoyl group, a mono- or di-lower alkylamino group, a mono- or di-lower alkanoylamino group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, sulfamoyl group and a mono- or di-lower alkylsulfamoyl group; R^3 is (1) an aryl group which may be substituted by at least one selected from cyano group, nitro group, amino group, a halogen atom, trifluoromethyl group, carboxyl group, hydroxyl group, carbamoyl group, a mono- or di-lower alkylamino group, a mono- or di-lower alkylamino-lower alkyl group, a mono- or di-lower alkylcarbamoyl group, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group, a lower alkanoyl group, a lower alkanoyloxy group, a lower alkanoyloxy-lower alkyl group, sulfo group, a lower alkylthio group, a lower alkylthio-lower alkyl

group, a lower alkylsulfonyl group, a lower alkylsulfamoyl group and a lower alkylsulfinyl group, (2) a heterocyclic group which may be substituted by at least one selected from oxo group, cyano group, nitro group, amino group, a halogen atom, carboxyl group, hydroxyl group, formyl group, carbamoyl group, a mono- or di-lower alkylamino group, a N-lower alkyl-N-cyclo-lower alkylamino group, a mono- or di-lower alkylamino-lower alkyl group, a mono- or di-lower alkylcarbamoyl group, a lower alkyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a lower alkoxy-lower alkyl group, a lower alkoxycarbonyl group, a lower alkanoyl group, sulfo group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkylsulfamoyl group, a lower alkylsulfinyl group and a heterocyclic group, or (3) a alkyl group which may be substituted by at least one selected from hydroxyl group, cyano group, carboxyl group, carbamoyl group, amino group, a mono- or di-lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, hydroxyamino group, a mono- or di-lower alkylcarbamoyl group, trifluoromethyl group, a halogen atom, a lower alkoxy group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, sulfamoyl group, a mono- or di-lower alkylsulfamoyl group, a lower alkoxycarbonyl group and a heterocyclic group; and R^4 is (1) hydrogen atom, or (2) a lower alkyl group which may be substituted by a mono- or di-lower alkylamino group.

10. The use according to Claim 8 or 9, wherein R^1 is (1) a lower alkyl group which may be substituted by carboxyl group, a lower alkoxycarbonyl group or a heterocyclic group, (2) an aryl group which may be substituted by one or two halogen atoms, or (3) a heterocyclic group which may be substituted by a halogen atom, R^2 is (1) a lower alkyl group which may be substituted by carboxyl group, a lower alkoxycarbonyl group or a heterocyclic group, (2) a heterocyclic group which may be substituted by a halogen atom, or (3) an aryl group which may be substituted by one or two halogen atoms; R^3 is (1) a heterocyclic group which may be

substituted by one or two groups selected from amino group, a halogen atom, a lower alkyl group, a lower alkoxy group, a mono- or di-lower alkylamino group and a lower alkylthio group, or (2) an aryl group which may be substituted by amino group, a halogen atom, a lower alkyl group, a lower alkylthio group, a lower alkoxy group or a mono- or di-lower alkylamino group; and R^4 is hydrogen atom or a lower alkyl group.

11. The use according to Claim 10, wherein R^1 is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3) a lower alkyl group substituted by a tetrazolyl group, (4) a phenyl group which may be substituted by one or two halogen atoms, or (5) a thienyl group which may be substituted by a halogen atom; R^2 is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3) a lower alkyl group substituted by a tetrazolyl group, (4) a thienyl group which may be substituted by a halogen atom, or (5) a phenyl group which may be substituted by one or two halogen atoms; and R^3 is (1) a benzothienyl group which may be substituted by a halogen atom, (2) a phenyl group which may be substituted by a halogen atom, a lower alkylthio group, a lower alkoxy group or a di-lower alkylamino group, (3) a pyridyl group which may be substituted by a lower alkyl group, a lower alkoxy group or a di-lower alkylamino group, (4) a pyrimidinyl group which may be substituted by a di-lower alkylamino group or a lower alkylthio group, (5) a thienyl group which may be substituted by one or two lower alkyl groups, (6) thiopheno[3,2-b]pyridyl group, (7) benzofuryl group, (8) dihydrobenzofuryl group or (9) an indolyl group which may be substituted by a lower alkyl group.

12. The use according to Claim 11, wherein X is O or S; R^1 is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3) a phenyl group which may be substituted by one or two halogen atoms, or (4) a thienyl group which may be substituted by a halogen atom; R^2 is (1) a carboxyl-lower alkyl group, (2) a lower alkoxycarbonyl-lower alkyl group, (3)

a thienyl group which may be substituted by a halogen atom, or (4) a phenyl group which may be substituted by one or two halogen atoms; and R^3 is (1) a benzothienyl group which may be substituted by a halogen atom, (2) a phenyl group which may be substituted by a halogen atom, a lower alkylthio group, a lower alkoxy group or a di-lower alkylamino group, (3) a pyridyl group which may be substituted by a lower alkoxy group or a di-lower alkylamino group, (4) a pyrimidinyl group which may be substituted by a di-lower alkylamino group, (5) a thienyl group which may be substituted by a di-lower alkyl group, (6) thiopheno[3,2-b]pyridyl group, or (7) an indolyl group which may be substituted by a lower alkyl group.

13. A compound represented by the formula (I) wherein X is O, one of R^1 and R^2 is a thienyl group substituted by a chlorine atom, and the other is a carboxyl-lower alkyl group, a lower alkoxycarbonyl-lower alkyl group or a lower alkyl group substituted by a tetrazolyl group, and R^3 is a substituted or unsubstituted aryl group or a substituted or unsubstituted heterocyclic group, or a pharmaceutically acceptable salt thereof.

14. The compound according to Claim 13, wherein R^3 is (1) an aryl group which may be substituted by one or two substituents selected from a halogen atom, a di-lower alkylamino group, a lower alkylthio group and a lower alkoxy group, or (2) a heterocyclic group which may be substituted by one or two substituents selected from a halogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group and a mono- or di-lower alkylamino group.

15. The compound according to Claim 14, wherein one of R^1 and R^2 is a thienyl group substituted by a chlorine atom, and the other is a carboxyl-lower alkyl group or a lower alkoxy-carbonyl-lower alkyl group; the aryl group is phenyl group; and the heterocyclic group is a thienyl group, a pyridyl group, a

pyrimidinyl group, a benzothienyl group, a benzofuryl group, a dihydrobenzofuryl group, an indolyl group or a thieno-[3,2-b]pyridyl group.

16. The compound according to Claim 14, wherein R^3 is a phenyl group which is substituted by a halogen atom or a lower alkylthio group; a thienyl group which is substituted by one or two lower alkyl groups; a pyrimidinyl group which is substituted by di-lower alkylamino group; a benzothienyl group which may be substituted by a halogen atom; an indolyl group which may be substituted by a lower alkyl group; or a thieno[3,2-b]pyridyl group.

17. A compound represented by the formula (I) wherein X is S, one of R^1 and R^2 is a thienyl group substituted by a chlorine atom, and the other is a carboxyl-lower alkyl group, a lower alkoxycarbonyl-lower alkyl group or a lower alkyl group substituted by a tetrazolyl group, and R^3 is a substituted or unsubstituted heterocyclic group, where said heterocyclic group is selected from a pyridyl group, a pyrimidinyl group, a benzothienyl group, an indolyl group and a thieno[3,2-b]-pyridyl group, or a pharmaceutically acceptable salt thereof.

18. The compound according to Claim 17, wherein R^3 is a heterocyclic group which may be substituted by one or two substituents selected from a halogen atom, a lower alkoxy group, a mono- or di- lower alkyl group, a lower alkylthio group and a mono- or di-lower alkylamino group, where said heterocyclic group is selected from a pyridyl group, a pyrimidinyl group, a benzothienyl group, and a thieno[3,2-b]pyridyl group.

19. The compound according to Claim 18, wherein one of R^1 and R^2 is a thienyl group substituted by a chlorine atom, and the other is a carboxyl-lower alkyl group or a lower alkoxy-carbonyl-lower alkyl group; R^3 is a pyridyl group which may be substituted by a di-lower alkylamino group; a pyrimidinyl group

which may be substituted by a mono- or di-lower alkylamino group; or a benzothienyl group which may be substituted by a halogen atom.

20. 4-(5-Chlorothiophen-2-yl)-2-(2-benzo[b]thienyl)-thiazol-5-yl acetic acid,
5-(4-chlorophenyl)-2-(2-N,N-dimethylaminopyrimidin-5-yl)-oxazol-4-yl acetic acid,
4-(5-chlorothiophen-2-yl)-2-(4-methoxyphenyl)thiazol-5-yl acetic acid,
5-(5-chlorothiophen-2-yl)-2-(4,5-dimethylthiophen-2-yl)-oxazol-4-yl acetic acid,
4-(5-chlorothiophen-2-yl)-2-(2-N,N-dimethylaminopyrimidin-5-yl)thiazol-5-yl acetic acid,
4-(5-chlorothiophen-2-yl)-2-(2-N,N-dimethylaminopyridin-5-yl)thiazol-5-yl acetic acid,
5-(4-chlorophenyl)-2-(4-fluorophenyl)oxazol-4-yl acetic acid,
5-(4-chlorophenyl)-2-(2-benzo[b]thienyl)oxazol-4-yl acetic acid,
4-(5-chlorothiophen-2-yl)-2-(2-benzo[b]thienyl)oxazol-5-yl acetic acid,
5-(5-chlorothiophen-2-yl)-2-(2-N,N-dimethylaminopyrimidin-5-yl)oxazol-4-yl acetic acid,
4-(4-chlorophenyl)-2-(2-N,N-dimethylaminopyrimidin-5-yl)-thiazol-5-yl acetic acid,
5-(5-chlorothiophen-2-yl)-2-(2-benzo[b]thienyl)oxazol-4-yl acetic acid,
4-(4-chlorophenyl)-2-(4-methoxyphenyl)thiazol-5-yl acetic acid,
5-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazol-4-yl acetic acid,
5-(5-chlorothiophen-2-yl)-2-(6-fluorobenzo[b]thiophene-2-yl)oxazol-4-yl acetic acid,
5-(3-thienyl)-2-(2-benzo[b]thienyl)oxazol-4-yl acetic acid,
5-(5-chlorothiophen-2-yl)-2-(2-thieno[3,2-b]pyridyl)-

oxazol-4-yl acetic acid,
5-(3-fluoro-4-chlorophenyl)-2-(2-benzo[b]thienyl)oxazol-4-yl acetic acid,
5-(5-chlorothiophen-2-yl)-2-(2-benzo[b]thienyl)thiazol-4-yl acetic acid,
5-(5-chlorothiophen-2-yl)-2-(4-methylthiophenyl)oxazol-4-yl acetic acid,
4-(5-chlorothiophen-2-yl)-2-(4-fluorophenyl)oxazol-5-yl acetic acid,
5-(5-chlorothiophen-2-yl)-2-(4-chlorophenyl)oxazol-4-yl acetic acid,
4-(3-fluoro-4-chlorophenyl)-2-(4-methoxyphenyl)thiazol-5-yl acetic acid,
4-(5-chlorothiophen-2-yl)-2-(4,5-dimethylthiophen-2-yl)-thiazol-5-yl acetic acid,
4-(3-fluoro-4-chlorophenyl)-2-(4-fluorophenyl)thiazol-5-yl acetic acid,
4-(4-chlorophenyl)-2-(2-N,N-dimethylaminopyridin-5-yl)-thiazol-5-yl acetic acid,
4-(5-chlorothiophen-2-yl)-2-(4-N,N-dimethylaminophenyl)-thiazol-5-yl acetic acid,
5-(5-chlorothiophen-2-yl)-2-(N-methylindol-2-yl)oxazol-4-yl acetic acid,
5-(5-chlorothiophen-2-yl)-2-(4,5-dimethylthiophen-2-yl)-thiazol-4-yl acetic acid;
or a lower alkyl ester thereof;
or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a therapeutically effective amount of a compound as set forth in any one of Claims 13 to 20 in admixture with a therapeutically acceptable carrier or diluent.

22. Use of the compound as set forth in any one of Claims 13 to 20 for manufacture of a medicament for use in the prophylaxis and/or treatment for pollakiuria or urinary incontinence.

23. The use according to Claim 22, wherein the compound is as set forth in Claim 20.

24. Use of a compound as set forth in any one of Claims 13 to 20 for manufacture of a large conductance calcium-activated K channel opener.

25. The use according to Claim 24, wherein the compound is as set forth in Claim 20.

26. A large conductance calcium-activated K cannel opener comprising as an active ingredient the compound as set forth in any one of Claims 13 to 20.

27. The large conductance calcium activated K channel opener according to Claim 26, wherein the compound is as set forth in Claim 20.

28. A method for prophylaxis and/or treatment of pollakiuria or urinary incontinence which comprises administering an effective amount of the compound as set forth in any one of Claims 13 to 20 to a patient of pollakiuria or urinary incontinence or a patient who has a possibility of causing pollakiuria or urinary incontinence.

29. The method according to Claim 28, wherein the compound is as set forth in Claim 20.